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Sarcoidosis

MARTIN M. CUMMINGS
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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Sarcoidosis

MARTIN M. CUMMINGS
MAX MICHAEL, JR.

TABLE OF CONTENTS

DEFINITION 4

HISTORICAL 4

PATHOGENESIS 5

Epidemiology 5

Etiology 7

PATHOLOGY 11

CLINICAL FEATURES 15

Onset 15

Systemic Symptomatology 16

Organ Involvement 16

DIAGNOSIS 29

Laboratory Data 29

Skin Tests 30

Biopsy 31

Differential Diagnosis 32

COURSE 32

PROGNOSIS 35

TREATMENT 36

SUMMARY 37

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THE RENEWED INTEREST IN SARCOIDOSIS in the past decade has resulted in a veritable deluge of case reports, review articles and monographs in the world literature. This monograph is intended to bring to the reader a summary of present-day concepts of the cause and pathogenesis of sarcoidosis. The review of the clinical manifestations should acquaint him with the more general features of the disease process as it is now understood. No attempt has been made to include all of the recorded oddities and esoteric clinical findings which are a part of the truly flooded literature. Where the reader's interest is aroused in a particular phase, it will be profitable for him to pursue this angle—be it etiologic, clinical, etc.—in greater detail by referring to the various references listed in the bibliography.

DEFINITION*

Sarcoidosis is a chronic granulomatous disease or syndrome of unknown origin. Many names have been assigned to this entity. Among them have been *Boeck's sarcoid, lupus pernio, benign lymphogranulomatosis, osteitis tuberculosa* and *uveoparotid fever.* In this monograph, *sarcoidosis* will be used to include the whole gamut of syndromes and manifestations which are part of the clinical picture. The disease is characterized histologically by the presence of epithelioid cell tubercles, not unlike the hard tubercles of tuberculosis and other infectious granulomas, and most commonly it involves the lymph nodes, lungs, skin, liver, spleen, eyes and phalangeal bones. The reaction may be localized (sarcoid), but the term "sarcoidosis" implies systemic involvement. Symptoms and signs, when present, reflect the changes which have occurred in the tissues and organs involved.

The giant cells present in the lesions may contain inclusion bodies (Schaumann and asteroid bodies). The epithelioid cell collection occurs in small miliary clumps and rarely shows necrosis. The tubercles are usually of uniform size within an organ, but they may form a constituent part of an infiltrating granulomatous mass. Healing takes place by fibrosis and hyalinization. Hyperglobulinemia, hypercalcemia and hypercalciuria may occur. Other laboratory features of the disease include leukopenia, eosinophilia and anemia. Anergy of the skin occurs in a large percentage of patients. Consequently, the response to the intracutaneous tuberculin test is frequently, but not always negative.

HISTORICAL

Sarcoidosis was first described by Jonathan Hutchison (1875), who observed the granulomatous skin lesions and called the disease "Mortimer's malady" after a patient he had studied (1). A similar case report was presented by Besnier (2) in France in 1889. Besnier chose the name "lupus pernio," since he considered the skin lesions to be a form of tuberculosis (lupus vulgaris).

However, it was not until 1899 that Caesar Boeck (3), a Norwegian physician, described in a series of reports the first clear

*Modified from the National Research Council Subcommittee on Sarcoidosis (1958).

clinical and anatomic description of the systemic disease. He pointed out that the disease might be manifest in the lungs and suggested that the lesions might be differentiated from tuberculosis. The modern name of the disease comes from his description of the cells comprising the lesion as being "sarcomatous" in appearance. Boeck's concept of the nature of the disease was that it was in some way related to benign sarcomas. Therefore, he offered the name "multiple benign sarkoid." He later abandoned this concept of its neoplastic nature and became an advocate of the tuberculous origin after having revealed the presence of acid-fast bacilli within the nasal mucosa of a patient. Thereafter he changed the name of the disease to "benign miliary lupoid." One might speculate that this patient had leprosy.

In 1909 a Danish ophthalmologist, Heerfordt (4), presented a description of a symptom complex of chronic iridochoroiditis and bilateral parotitis which was sometimes accompanied with facial paralysis. He called this "fibris uveoparotidea subchronica," and he considered the involvement of the eyes and parotids to be due to inflammatory changes within these organs and suggested that condition was a result of an infection due to some unknown micro-organism. This involvement, too, is now considered a part of the sarcoidosis complex.

In 1914 Schaumann (5) presented convincing evidence that the disease states described by Besnier and Boeck were identical, and he pointed out that sarcoidosis was primarily a disease of the lymphoid system. After careful histologic examination of various tissues, he suggested that the lesions of the skin, lymph nodes and other organs were essentially the same manifestations of a single disease. He retained the name "lupus pernio" because he considered the condition to be a form of tuberculosis. However, after failing to demonstrate tubercle bacilli in tissues, he chose the name "lymphogranulomatosis benigna" (6). One of the inclusion bodies within the giant cells still bears his name.

During the past three decades, a more complete clinical and biologic description of sarcoidosis has been offered by Freiman (7) and by Longcope and Pierson (8).

PATHOGENESIS

Epidemiology

An accurate account of the pathogenesis of sarcoidosis is difficult to present in the absence of any known etiologic agent or

FIG. 1.—Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis. (From Cummings, M. M., *et al.*: Concepts of epidemiology of sarcoidosis, Postgrad. Med. 19:437, 1956.)

agents. Although the disease was first described in Scandinavia, it is now known to occur in most parts of the world, being most prevalent in the North Temperate Zone. While it seemed to occur almost exclusively in Caucasians in Europe, Michael and his associates (9) have demonstrated a striking predilection for the Negroes in the United States. In a study of 300 cases collected from among the military personnel of World War II, they found a 17:1 ratio for Negroes as compared to whites. In a later study of sarcoidosis in veterans, reported by Cummings and his associates (10), the disease was 13 times more common in Negroes than in whites. In both these studies, most of the patients were born in rural areas. The rural distribution has also been noted by European investigators. All of these reports indicate that the distribution of cases does not conform to that of tuberculosis. The heaviest concentration of cases in the United States came from the southeastern and northeastern states (11) (Fig. 1).

While there are no data for precise incidence and prevalence, it seems that, in population groups which have been carefully studied, the disease occurs in from 1 to 4 persons per 10,000 young adults. It occurs very uncommonly in children and rarely makes its first appearance in the elderly.

Sarcoidosis has been reported in family groups and on rare occasions in identical twins. It is difficult to interpret these findings because twins and family groups may well be exposed to the same environmental influences. Although it has been suggested that the disease occurs more commonly among farmers and outdoor workers, there is still no reliable proof of this relationship.

Many reports in the literature suggest that sarcoidosis occurs with equal frequency in males and females, although there is some indication that young white females may have a somewhat higher incidence. It has also been suggested that sarcoidosis becomes manifest in the pregnant woman more often than expected.

Etiology

Since the cause of sarcoidosis has never been established unequivocally, there is still much controversy concerning the possible relationship of the disease to tuberculosis. Those who argue that sarcoidosis is an aberrant form of tuberculosis base their case on the fact that the microscopic lesions have many simi-

FIG. 1.—Geographic distribution of birthplaces of 1,194 veterans with sarcoidosis. (From Cummings, M., *et al.*: Concepts of epidemiology of sarcoidosis, Postgrad. Med. 19:437, 1956.)

larities. They explain the high frequency of negative tuberculin reactions and the absence of acid-fast bacilli in the lesions on the basis of some unusual immunity to the tubercle bacillus. Thus Jadassohn (12), in 1919, tried to explain the anergy to tuberculin in sarcoidosis as a "positive anergy." He believed that the formation of antibodies was followed by the production of anticutins in the serum which diminished the tuberculin reaction. Uehlinger (13), in 1942, considered the hyposensitivity to tuberculin to be a constitutional factor. Neither viewpoint has been supported by convincing experimental evidence.

More recent investigators tend to oppose the hypothesis that sarcoidosis is a form of tuberculosis. Their arguments rest on the following points: (*a*) a large number of well-conducted bacteriologic studies have failed to demonstrate the presence of tubercle bacilli within the lesions; (*b*) the disease has not been transmitted from the lesions of man to animals; (*c*) the presence of anticutins or antibodies to tubercle bacilli in sera from patients with sarcoidosis has not been confirmed; (*d*) there is a low incidence of tuberculin reactions in patients with sarcoidosis and a high incidence of Kveim reactions when extracts of involved lymph nodes, or of spleen, of patients with sarcoidosis are used for intradermal testing; and (*e*) the unique geographic distribution of the disease differs from that of tuberculosis.

Some workers have suggested that sarcoidosis may be related to syphilis and leprosy, as well as to various other chronic bacterial infections. However, no convincing support of these concepts has been forthcoming.

In 1950 Löfgren and Lundbäck (14) suggested that viruses might be responsible for the disease. The tendency toward leukopenia and a low order of tuberculin allergy have been considered to be analogous to the situation which occurs with measles. Again, however, laboratory studies testing these hypotheses have, so far, been unrewarding.

Some investigators have suggested that the tissue lesions might result from mycotic infection. In 1946 Tornell (15) postulated that sarcoidosis was a chronic form of moniliasis. Although the x-ray lesions are similar, histopathologic and microbiologic proof of this relationship has not been forthcoming. However, the granulomata of histoplasmosis and other mycoses are very difficult to distinguish from sarcoidosis.

The concept that sarcoidosis may be an allergic disease similar to rheumatic fever, periarteritis nodosa and lupus erythematosus was reviewed by Van Rijssel (16) in 1947 and by Teilum (17) in 1948. This hypothesis is supported by several

clinical observations, such as (*a*) the occurrence of transient joint pains, (*b*) eosinophilia in the blood and the presence of young eosinophils in early granulomas, (*c*) the occurrence of granulomas in the walls of blood vessels and (*d*) the occurrence of nodules in the heart similar to those seen in rheumatic fever. Teilum (17) suggests that there is an allergic hyperglobulinosis of the reticuloendothelial system produced by repeated stimulation of the immune mechanism. Thus, the allergic theory somewhat overlaps the tuberculous theory of origin—one suggesting reactions more related to the immediate type of hypersensitivity, the other suggesting the delayed type of hypersensitivity reaction.

Among the most original investigations are those of Refvem (18) on localized sarcoid granulomas. He has shown that epithelioid cell granulomas may occur in local sites after exposure to a variety of particulate matter. Refvem has suggested that particles of calcareous spar might give rise to sarcoidosis granulomas after their introduction into the body by inhalation or trauma. Thus he believes that some cases of sarcoidosis represent a more or less generalized foreign-body reaction. Gentry and his associates (19) suggest that certain soil types (particularly red-yellow podsolic soil) might in some way induce sarcoidosis granulomas. This suggestion followed their epidemiologic observation that patients with sarcoidosis in the United States were born and have spent their major lifetime living in the southeastern portion of the country, where this soil type is predominant.

On the basis of an epidemiologic study of 1,194 cases of sarcoidosis occurring among American veterans, Cummings and his associates (10, 11) were impressed with the close correlation between the birthplaces of these patients and the distribution of forests. They observed that the heaviest concentration of cases occurred in the most densely pine-forested areas (Fig. 2). Laboratory studies revealed that pine pollen had acid-fast characteristics similar to those of the tubercle bacillus. They also observed that pine pollen contained an acid-fast lipid which, on intradermal and subcutaneous injection, induced the formation of localized epithelioid cell granulomas in guinea pigs. However, they did not succeed in producing systemic involvement. On the basis of these epidemiologic and laboratory observations, these investigators have suggested that some cases of sarcoidosis might result from exposure to pine pollen—i.e., there might be a hypersensitivity phenomenon. More recent epidemiologic studies by Wijkstrom and Wallgren (20) in Sweden and by

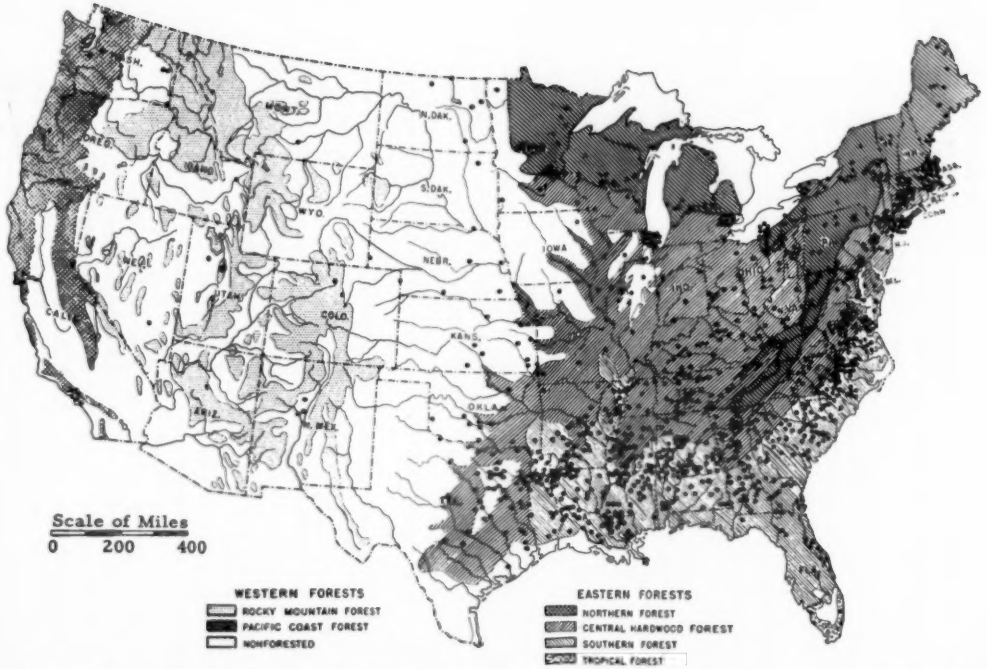


FIG. 2.—Geographic distribution of birthplaces of 1,194 veterans with sarcoidoses correlated with distribution of forests in the United States. (From Cummings, M. M., *et al.*: Concepts of epidemiology of sarcoidosis, Postgrad. Med. 19:437, 1956.)

Hurwitz (21) in Denmark have confirmed the correlation of the higher prevalence of sarcoidosis in the more dense coniferous forested areas of these countries. Additional studies of the epidemiology of sarcoidosis in other parts of the world are needed.

PATHOLOGY

Sarcoidosis may involve almost any organ or tissue of the body. Most commonly the lymph nodes are involved. The hilar or tracheobronchial lymph nodes are affected in nearly all cases. This is followed, in order of frequency, by involvement of the lungs, liver, spleen, skin, eyes and bones. Lesions may be found in the vascular system, the kidneys and the gastrointestinal tract. Less frequently the central nervous system, the glands of internal secretion and voluntary muscles may be invaded.

Microscopically, the hallmark of sarcoidosis is the epithelioid cell granulomas, which appear as small nodules or hard tubercles. Each granuloma consists of tightly packed epithelioid cell clusters, regular in outline and having interspersed multinucleated giant cells. Lymphocytes and fibroblasts may be seen at the periphery. Caseation necrosis does not occur. The giant cells frequently show inclusion bodies, known as Schaumann bodies. Birefringent bodies similar to those seen in the sarcoid lesion have been described in certain forms of early tuberculosis and beryllium disease. Thus it may be extremely difficult to distinguish between the lesion of sarcoidosis and that seen in early tuberculosis, beryllium disease and certain fungus diseases. Asteroid bodies may be seen in giant cells. They have a diameter of 30–50 μ and appear as granular structures with sharp peripheral raylike filaments. The crystal shape of the lesion and the presence of calcium and iron within it suggest that it may represent a salt deposit. Asteroids are usually eosinophilic. They are considered, by some investigators (22), to be protein precipitates. They are not specific for the diagnosis of sarcoidosis. The nature of these inclusion bodies has suggested different etiologic concepts to different workers. The characteristics of the sarcoid tubercle are shown in Figures 3, 4, 5 and 6.

The lesions may appear to be progressive, static or retrogressive. Healing appears to take place through fibrosis and hyalinization. In any given area the cluster of epithelioid tubercles results in tissue of monotonous appearance. Coalescence of tubercles may produce large sarcoid "tumors." The regressive

FIG. 2.—Geographic distribution of birthplaces of 1,194 veterans with sarcoidoses correlated with distribution of forests in the United States. (From Cummings, M. M., *et al.*: Concepts of epidemiology of sarcoidosis, Postgrad. Med. 19:457, 1956.)

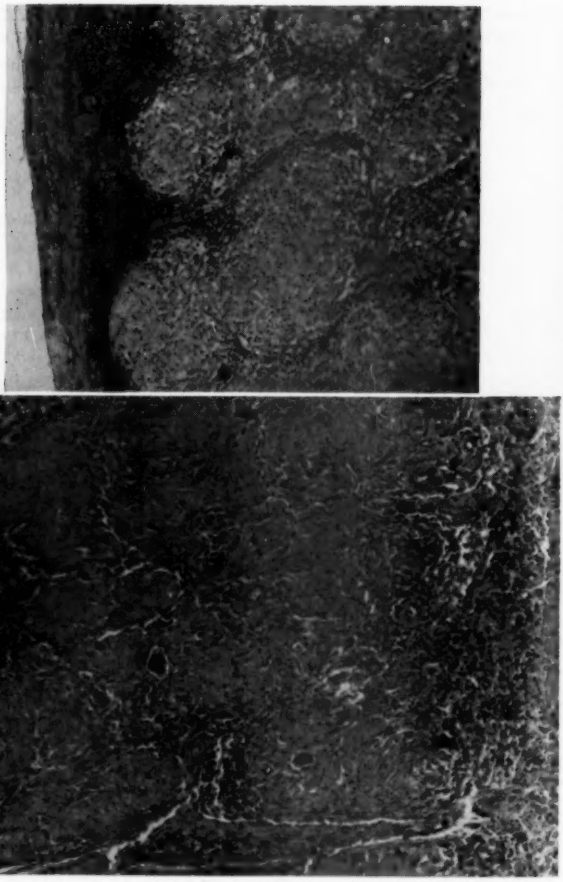
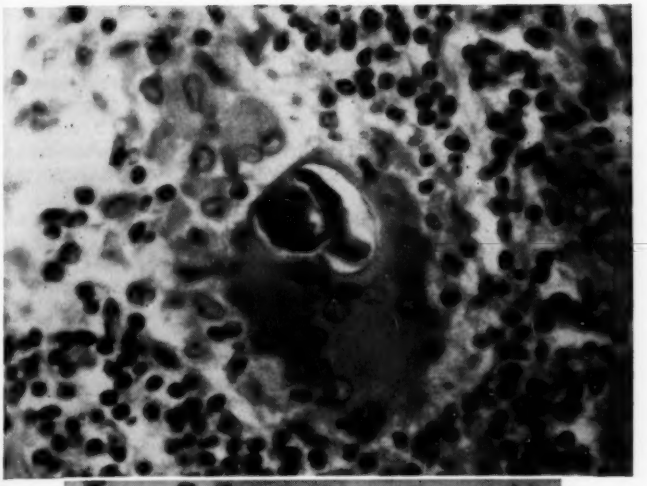


FIG. 3 (*top*).—Section of lymph node showing sarcoid granulomas replacing normal structure. Note the absence of caseation necrosis. The capsule and a small amount of lymphoid tissue are seen at one edge.

FIG. 4 (*bottom.*)—An aging lesion showing hyalinization and replacement of epithelioid tubercles by fibrous tissue. Reduced from × 100.



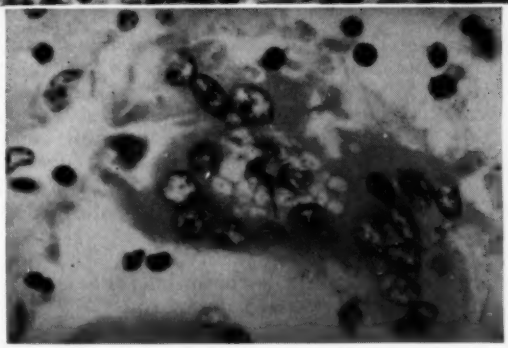


FIG. 5 (*top*).—Giant cell containing refractile inclusion as described by Schaumann. Reduced from × 400.

FIG. 6 (*bottom*).—Giant cell containing asteroid body; from a patient with sarcoidosis. Note the radial inclusions surrounded by vacuoles containing granular material.

changes have been described by Ricker and Clark (23) as fibrinoid necrosis, since the affected areas of the lesions present a fibrillar structure, seen best under high magnification and through the use of special stains (hematoxylin–van Gieson). Necrotizing arteriolitis is often a prominent feature of the histologic picture.

Lesions in the lungs may be limited to isolated tubercles in the bronchial tree and at the alveolar wall junctions. In the more advanced stages of the disease, the lesions may be seen as

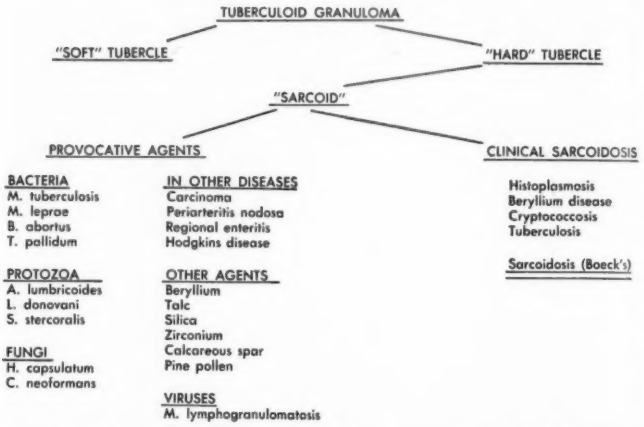


FIG. 7.—Schematic presentation of the sarcoid tubercle. (Modified after Refvem.)

infiltrating granulomatous masses in the lung or as small miliary epithelioid cell clusters scattered throughout.

Sarcoid-like granulomas have been observed in certain forms of Hodgkin's disease (24), in certain ovarian tumors (25) and in the regional lymph nodes in various forms of carcinoma (26). These findings have suggested that the sarcoid granuloma may be a specific response to a wide variety of stimuli. Indeed, Refvem (18) and Michael (27) have seriously entertained the concept that sarcoidosis may be a syndrome rather than a specific disease entity. If one adds to this the observation that similar lesions may be seen in lymphogranuloma inguinale (28)

and in certain protozoal and parasitic diseases (29), the syndrome concept becomes more attractive.

Figure 7 represents schematically the various agents which may evoke the histologic appearance as well as the syndrome of sarcoidosis.

Since the diagnosis of sarcoidosis usually cannot be made without demonstration of the characteristic pathologic features in some tissue, the delineation of the lesion becomes of great importance. However, it must be remembered that, even with histopathologic examination, it is often impossible to arrive at an unequivocal diagnosis. Autopsy studies have revealed that, at times, involvement of the lymph nodes thought to be due to sarcoidosis could not be differentiated from Hodgkin's disease, lymphosarcoma, histoplasmosis and noncaseating tuberculosis. The skin lesions may be confused with lupus, tuberculosis, syphilis and rheumatoid arthritis. Thus, although histopathology is extremely valuable in assisting in diagnosis, it does not always prove to be absolute in its accuracy.

CLINICAL FEATURES

Although sarcoidosis has certain rather characteristic clinical features, it is a disease of protean manifestations. The features in the individual patient depend, in part, on the sites affected, the extent of involvement and the stage in the development of the lesions. One could perhaps paraphrase the old axiom, "to know syphilis is to know medicine," to now state, "to know sarcoidosis is to know granulomatous diseases."

Onset

Sarcoidosis usually commences in an insidious manner and without a regular and orderly sequence of involvement of the various organs. Hence, the initial clinical manifestations are varied. Most often, symptoms referable to the lungs, eyes, skin or lymph nodes first call attention to the disease. Various hematologic disorders, unexplained fever and unexplained weight loss may be the presenting features. In many patients, asymptomatic sarcoidosis first comes under consideration as result of findings in routine X-ray of the chest (30).

Although the syndromes produced by involvement of the in-

dividual organ systems will here be considered separately, it must be realized that any combination may occur and that there may be varying degrees of affection of a particular organ. There is no "classic picture of sarcoidosis" and no routine sequence of organ involvement.

Systemic Symptomatology

Fever, if present, is usually low grade, with daily spikes to 100°; however, in some cases the onset of disease may be abrupt, with daily temperature elevations to 104°. In general, there is rarely fever of any significant degree and, when it is present, it occurs during the periods of greatest activity of the disease.

Malaise, weight loss and easy fatigability are common complaints but are nonspecific in nature. In a patient who has had sarcoidosis for a number of years, the assessment of the continuing symptoms may be quite difficult, as it is in any chronically ill patient.

Organ Involvement

Lungs.—The lungs are involved in approximately 90% of the patients with sarcoidosis. This figure would probably be increased with longer study of individual cases and with the use of "blind" biopsy of the lungs. In contradistinction to tuberculosis, the hilar lymph nodes in sarcoidosis are enlarged in many cases. This finding may precede the pulmonary infiltration, appear concurrently with it or make its appearance after the infiltrates have been recognized; it may at times be the sole intrathoracic abnormality in sarcoidosis (31). Enlargement of the hilar nodes, usually bilateral, produces a roentgen picture varying from a slight increase in the size of the hilar regions to huge lobulated adenopathy, the so-called "potato nodes." The right paratracheal node is often enlarged. Although adenopathy usually causes no symptoms, it may on rare occasions produce bronchial obstruction, atelectasis and subsequent suppuration through pressure on neighboring structures (32). Hilar lymph node enlargement without pulmonary infiltrates recedes at variable intervals, but usually within a year. Other symptomatology associated with hilar lymphadenopathy and sarcoidosis is discussed below.

FIG. 8 (*left*).—Bilateral hilar lymphadenopathy producing appearance of "potato nodes."
FIG. 9 (*right*).—Diffuse infiltrates throughout all lung fields seen by x-ray in a patient with few pulmonary complaints.

Infiltration of the pulmonary parenchyma is responsible for a variety of clinical and radiologic pictures. The lesions are usually bilateral and symmetrical (33, 34, 30). Diffuse, discrete miliary densities of about 1 mm. in size result from coalescence of the individual tubercles. These lesions are usually scattered widely throughout the lungs, mimicking miliary tuberculosis, but may be restricted to localized areas, such as the midzonal regions. They may regress without scarring or may coalesce and heal with fibrosis, resulting in permanent disability. When small infiltrates exist alone, the patient is usually without pulmonary symptoms. It is apparent that any of the numerous diseases that produce such miliary densities must be considered in the differential diagnosis.

Diffuse pulmonary nodulation results from coalescence of the miliary densities. These densities, varying in size from 3 to 5 mm., may be localized to any segment or may occur in random manner throughout the lungs. Although there is often some diminution in respiratory function, it is striking to see extensive disease in some patients who are completely asymptomatic. Physical findings are sparse. Occasional fine inspiratory rales or scattered wheezes may be noted. Healing of these lesions usually results in varying degrees of pulmonary fibrosis. Depending on the extent and location of the fibrosis, some disability will result from the healing. Diffuse infiltration, a fine reticular pattern or localized infiltrate with variable amounts of scattered fibrosis may be seen. As healing takes place, additional fibrosis often ensues (34). Such fibrosis may be accompanied by varying degrees of emphysema, bullae and severe respiratory incapacity (35).

One occasionally sees relatively young patients with diffuse pulmonary fibrosis without any obvious pre-existing etiologic factors. It is interesting to speculate whether such cases represent healed but otherwise unrecognized sarcoidosis. An unusual type of pulmonary disease is represented by large, relatively discrete, nodules which may resemble metastatic carcinoma (32).

Although it is convenient to attempt classification of the pulmonary findings on the basis of roentgenologic features, this often proves fruitless. Any combination of reticulation, infiltration, nodulation, fibrosis and emphysema may be seen in the same patient. Representative chest x-rays are shown in Figures 8, 9, 10 and 11.

Symptoms attributable to pulmonary disease are quite variable. The paucity of symptoms and physical signs in the face of

FIG. 10 (*left*).—Roentgenogram showing discrete nodulation and reticular appearance of lung fields in a patient with sarcoidosis. Hilar markings are accentuated.

FIG. 11 (*right*).—Extensive pulmonary fibrosis and inflammatory response seen by x-ray in a patient with long-standing sarcoidosis and repeated pulmonary infections.

widespread pulmonary infiltration has often been alluded to. However, it is usual for malaise, slight nonproductive cough and anorexia to be noted. As pulmonary function is compromised, dyspnea may be present. With extensive infiltrations, fibrosis and emphysema, the cough and severe dyspnea may assume major proportions. When there are large areas of fibrosis, emphysema or bronchiectasis, productive cough and hemoptysis may occur. Physical signs depend on the extent and type of pulmonary disease, but in general they are surprisingly few in the face of the major disease.

To assess activity of sarcoidosis on the basis of its roentgen appearance is fraught with difficulties. Even though the picture may be consistent with diffuse fibrosis alone, residual areas of active sarcoidosis may be present many years after onset of the disease. A consideration of other factors (to be discussed later, under Diagnosis) may shed light on the problems of activity presented by the individual case. Sarcoid tubercles rarely involve the pleura, but pleural effusion per se is an occasional finding (36). Bronchial invasion, usually asymptomatic, may be detected on biopsy.

The abnormalities of pulmonary function in sarcoidosis are quite variable. The extent of the basic lesions in the alveolar walls and perivascular areas apparently determines the degree of impairment of oxygen-diffusing capacity. Alveolar-capillary block may be detected in advanced cases of sarcoidosis (37). Paradoxically, there is often little correlation between the appearance of the lung on x-ray and the actual measurements of ventilation-perfusion efficiency. Patients with peripheral lesions without lung scarring may have normal function at rest. When generalized pulmonary fibrosis occurs, impaired ventilatory function (hyperpnea at rest) is readily detected. Hilar lymphadenopathy has little influence on ventilatory capacity unless there is mechanical obstruction of the airway. On occasion, particularly in patients with long-standing disease, the respiratory pattern of pulmonary emphysema will prevail. Obliteration of the pulmonary vascular bed and anoxia contribute to the development of pulmonary hypertension and cor pulmonale (35). Dyspnea and cyanosis become prominent features when such changes occur. These findings also may suggest myocardial involvement. Electrocardiograms should always be a part of the clinical examination of the patient.

Bilateral hilar lymphadenopathy syndrome.—The occurrence of bilateral hilar lymphadenopathy as an early manifestation of sarcoidosis is well recognized. However, until recent

years, most patients with this abnormality were considered to have tuberculosis, after lymphoma was excluded. Careful biopsy studies and long-range observation have strengthened the current thoughts (38, 39).

The bilateral hilar lymphadenopathy syndrome occurs most commonly between the ages of 25 and 30 years and predominantly in females. In over half the cases in one series, erythema nodosum was present at the onset of the illness. In an occasional patient, the hilar adenopathy precedes the skin eruption. Low-grade fever is usually present and persists concurrently with the erythema nodosum. In patients with the hilar syndrome and erythema nodosum, pain and swelling of the joints, especially the ankles, are common. These symptoms usually subside within 2 or 3 weeks (40). Contrariwise, in those without erythema nodosum, joint pains are unusual. Indeed, these patients are usually asymptomatic, with their disease most often being discovered by routine x-ray examination. An elevated sedimentation rate and eosinophilia are common findings, particularly in the patients with erythema nodosum. Symmetrical enlargement of the hilar nodes is obviously a *sine qua non* for the diagnosis of the bilateral hilar syndrome. Paratracheal cervical adenopathy may also occur.

The diagnosis of sarcoidosis in patients with the bilateral hilar lymphadenopathy syndrome depends on the application of the Kveim test and/or the demonstration of sarcoid tissue in an excised lymph node. Sometimes no peripheral nodes will be palpable and the scalene node must be biopsied.

In a series of 212 patients studied by Löfgren (38), parenchymal pulmonary infiltrates were present in 13% at the initial examination and developed later in an additional 25%. The prognosis in patients with the bilateral hilar syndrome is generally favorable; and in this series of 212 patients, who had enlarged bilateral hilar lymph nodes and erythema nodosum, complete clearing of hilar and pulmonary lesions occurred in 64% within 1 year and in 91% in 2 years. In only 8% did the parenchymal lesions assume chronicity. In those patients without erythema nodosum, the prognosis was not quite so good, 27% showing a tendency to chronicity at the end of 2 years.

Other manifestations—e.g., cutaneous lesions and uveoparotitis—were infrequently encountered. Löfgren believes that the bilateral hilar lymphadenopathy syndrome, particularly that accompanied by erythema nodosum, represents the earliest stage of sarcoidosis—i.e., primary pulmonary sarcoidosis.

Treatment is symptomatic. Bed rest is indicated only during

the acute febrile stage of the disease. Where joint pains are troublesome, salicylates are often helpful. There seems to be little place for the use of adrenal steroids in the therapy of this group. However, when bronchial obstruction results from enlargement of the lymph nodes or other evidence of extension develops, steroid therapy may be helpful.

LYMPH NODES AND SPLEEN.—Enlargement of peripheral lymph nodes is probably the most frequent manifestation of sarcoidosis. Most commonly, the nodes in the cervical chain are enlarged, but any group may be so affected. The nodes are discrete, nontender and often are of a rubbery consistency (30). They may wax and wane in size, but they never ulcerate or involve the skin, as may happen with tuberculous lymph nodes. The lymph nodes offer one of the most accessible sources for biopsy to demonstrate sarcoid tissue. Involved nodes may be only pea sized, but their small size should be no deterrent to their use for diagnostic biopsy. The association of peripheral and intrathoracic lymphadenopathy is a common finding.

The spleen is moderately enlarged in over 25% of the cases. However, in autopsy series, it has been involved with sarcoid granulomas in over 70% of the cases. The spleen is usually asymptomatic, but its involvement may be the cause of a dragging, dull sensation in the left upper quadrant, particularly where the organ is unusually large. Various hematologic disorders, although somewhat uncommon, have been attributed to splenic involvement. Among these are hemolytic anemia, leukopenia and thrombocytopenic purpura. Splenectomy has produced beneficial effects, although the adrenal steroids have accomplished similar results in most patients having such involvement.

SKIN.—The first descriptions of what is now known as sarcoidosis were of cutaneous lesions. While not common, occurring, as they do, in approximately 20% of cases, such lesions do offer some prognostic clues and may furnish the only histologic proof of suspected sarcoidosis. They are seen more frequently in Negroes. A variety of names have been attached to the different types of lesions and their locations; however, enumeration of these is not profitable for this discussion. Skin lesions may develop at any time in the course of sarcoidosis and may actually precede the appearance of other manifestations by several years (31, 41).

There may be localized skin lesions which have the clinical and histologic features of those seen in the systemic disease but with none of the associated findings, such as iritis, pulmo-

nary disease, etc. Such lesions develop many years after trauma (18). It is best to call such abnormalities "localized sarcoids" and reserve the term "sarcoidosis" for the systemic disease. In many cases, such a development does not occur.

Erythema nodosum, while not representing true infiltration of the skin by sarcoid tissue, is one of the cutaneous manifestations to be sought. These painful red nodules, occurring principally on the shins, are part of a variety of hypersensitive responses (e.g., coccidioidomycosis, streptococcal infections, etc.) and probably have the same connotations in sarcoidosis. They occur as a part of the bilateral hilar lymphadenopathy syndrome, which probably represents the earliest stage of sarcoidosis.

The basic skin lesions are nodules, macules, plaques and localized tumors. They are usually firm with an elastic consistency and have a tendency to clear in the center with a spread to the periphery. On blanching a nodule, a yellowish color is sometimes noted. There is no ulceration, and healing usually is not accompanied by scarring. The lesions usually are multiple and have a predilection for the face, especially around the eyelids, the bridge of the nose, the shoulders, extensor surfaces of the extremities and the trunk. In general, the more chronic and persistent plaques and nodules are associated with later stages of pulmonary infiltration; whereas, in the patients with transient plaques, radiologic clearing of the lungs is common. Representative skin lesions are shown in Figures 12 and 13.

Sarcoid-like granulomas may develop at the site of trauma or surgical operations. The lesions have rarely extended from these sites and thus may not be related to the systemic disease sarcoidosis. On the other hand, existing scars have been noted to change in appearance, developing sarcoid granulomas after the disease has been known to be present in other organs. Sarcoid nodules have also appeared at the site of tattoos; and in one case a nodule extended from this site to regional lymph nodes and ultimately involved the lungs. Such occurrences, while rare, provoke much thought concerning etiologic agents.

EYES.—Ocular sarcoidosis may run the gamut from minor lesions, detected only by special means, to a florid iridocyclitis with ensuing blindness. Involvement of the eyes occurs in approximately 15% of the cases of sarcoidosis, there being a higher incidence in members of the Negro race.

Iridocyclitis is the commonest manifestation and may be bilateral or unilateral. The onset may be sudden, with dimness

FIG. 12 (*left*).—Scattered nodules and plaques seen over anterior surface of lower extremities. Biopsy of skin revealed epithelioid cell granulomas.

FIG. 13 (*right*).—Raised, discrete, rough sarcoid granulomas seen on the skin of the posterior aspect of the upper extremity near the buttock.

of vision, ocular pain and lacrimation. There is circumcorneal injection and haziness of the anterior chamber. In such instances, complete clearing usually occurs within 6 months. In the more chronic form, however, the onset is less dramatic and indeed may be asymptomatic. Grayish-white particles floating in the aqueous humor may become adherent to the cornea, producing the so-called "mutton fat" deposits. Anterior and posterior synechiae, cataracts and glaucoma may occur. Since the lesions heal with scarring, the potential visual disability is apparent. Asymptomatic nodular lesions on the iris may be noted when no other ocular manifestations are present. Slit-lamp examination is necessary for their detection.

Conjunctival involvement in the form of nodular lesions or of acute nonspecific conjunctivitis may occur. Enlargement of the lacrimal glands may also be noted (33).

Other evidences of sarcoidosis throughout the body usually exist and should be sought. Particularly when iridocyclitis is present is there apt to be chronicity of the generalized disease. Enlargement of the parotid glands, frequently accompanied by fever and associated Bell's palsy, has been called Heerfordt's syndrome or uveoparotid fever. The classification, long debated, is now clearly that of sarcoidosis (33). Steroid therapy is mandatory when eye involvement occurs, since irreparable changes may develop rapidly, leading to blindness.

BONES.—Under the term "osteitis multiplex cystoides," Jungling described a type of bone lesion now recognized as being a finding in a limited number of cases of sarcoidosis. Osseous sarcoidosis, usually asymptomatic, is of variable occurrence, but the true incidence is probably between 10 and 20%. Characteristically, the phalanges of the hands and feet are involved, the latter more commonly. The classic findings consist of punched-out lesions, which represent circumscribed collections of sarcoid tissue, with normal bone surrounding. A more diffuse involvement of the medullary cavity produces thinning of the cortex and a reticular pattern of the trabeculae. This results in a honeycomb or lattice-work configuration. Coalescence of these lesions may produce extensive bone destruction and mutilation. Rarely are bones other than the phalanges involved. The long bones, tarsal and carpal bones, vertebrae and mandible, among others, have been described as the site of the lesions (36).

Usually the process is asymptomatic but with extensive destruction; pain in the bones and pain and stiffness in neighboring joints may occur. As the sarcoidosis regresses, so do the

FIG. 13 (*right*).—Raised, discrete, rough sarcoid granulomas seen on the skin of the posterior aspect of the upper extremity near the buttock.

bone lesions, with healing taking place unless there has been extensive disruption of the cortex.

Although the bone lesions are not common, their presence lends weight to the diagnosis of sarcoidosis. Particularly is this true since these types of lesions occur exceedingly rarely, if at all, in tuberculosis, beryllium disease and histoplasmosis—diseases which may be confused clinically and histologically with sarcoidosis. Clubbed fingers are an extremely uncommon feature of this disease and in the experience of the authors have been seen only where chronic pulmonary suppuration resulted from the structural change of sarcoidosis.

JOINTS.—Acute polyarthritis, with a special predilection for the ankles, is a frequent accompaniment of the bilateral hilar lymphadenopathy syndrome with erythema nodosum. The reaction in the joints is manifested by swelling, heat, pain and tenderness. These signs usually persist for 1–2 weeks and, on subsiding, leave only residual soreness. Other than findings of joint effusion, there are no radiologic abnormalities. Transient joint pains without objective findings occur not infrequently in many patients with sarcoidosis.

A rarer type of a chronic arthritis may occur (43). Here a more protracted course with pain, swelling, stiffness and deformities may result. The peripheral joints are characteristically affected. Destruction of bone may occur but is not universal. Other manifestations of sarcoidosis are also present and usually direct attention to sarcoidosis as the possible cause of joint disability. These manifestations and the demonstration of sarcoid granulomas in the synovial tissues indicate that the arthritis is not secondary to invasion from the bone but represents a true manifestation of sarcoidosis. It is undoubtedly more common than recognized, many instances in the past having been considered as coexisting rheumatoid arthritis.

The sedimentation rate is usually elevated. The serologic tests for rheumatoid arthritis, rheumatic fever and lupus erythematosus are negative. Response to salicylate therapy may be gratifying. Steroids should be tried if such therapy fails.

MUSCLES.—Scattered granulomas of skeletal muscles have been noted. In general, the more extensive the disease, the more likely are these asymptomatic lesions to be found in random biopsy material. Although this may be of some diagnostic aid, the occurrence of the lesions in most series is of the order of 50–60%. Coalescence of the smaller granulomas will, in rare instances, produce large palpable collections of sarcoid tissue (44).

A peculiar type of myopathy was recently described by Harvey (45). These patients have profound weakness, muscle wasting, arthralgia, bouts of fever and "hard tubercles characteristic of those seen in sarcoidosis" in the muscles. No other evidences of systemic sarcoidosis were noted, which raises the question as to how positive one can be that this syndrome is a true part of the sarcoidosis picture.

HEART.—Sarcoid tubercles may develop throughout the myocardium (31). They are usually asymptomatic, but they can cause life-threatening arrhythmias. Stokes-Adams syndrome is a not uncommon manifestation. Varying degrees of heart block may result; sudden death has been recorded (46). Diffuse myocardial invasion, usually occurring in severe forms of the disease, may be responsible for cardiac decompensation. Although not related necessarily to myocardial sarcoidosis, cor pulmonale may ensue as a result of extensive fibrosis with subsequent pulmonary hypertension. Whenever the myocardium is so affected, adrenal steroids must be administered.

KIDNEYS.—As is true of all organs of the body, the kidneys may be involved, with scattered granulomas which are usually of little consequence clinically. On the other hand, hypercalcemia and hypercalciuria, which occurs in approximately 20–30% of the cases, may occasionally result in renal failure and may also be responsible for renal calculi. The frequency of hypercalcemia appears to be greater in patients in this country than in those studied in Great Britain and Scandinavia. Weakness, lassitude, hyposthenuria and azotemia are noted. There is often an absence of protein or formed elements in the urine. Although diffuse nephrocalcinosis may occur, the renal failure is most likely the result of the effects of hypercalcinosis on the kidney, much as in other hypercalcemic states. In those instances in which serial renal biopsies have been made, no change has been detected in the amount of nephrocalcinosis, although the hypercalcinosis and renal failure have improved with appropriate therapy (47).

The hypercalcemia results from an increased absorption of calcium from the alimentary tract. This may represent, among other things, an abnormal sensitivity to endogeneous vitamin D or the excessive production of a vitamin D-like substance. Adrenal steroid therapy corrects this effect, with a resulting increased fecal excretion, and decreased urinary excretion of calcium and a reversion of the serum calcium to normal levels. Concurrently with the fall in serum calcium levels, the nitrogen retention lessens, the hyposthenuria reverts, and, unless

permanent renal damage has developed, the symptoms of hypercalcinosis and azotemia abate.

CENTRAL NERVOUS SYSTEM.—In the course of uveoparotitis, compression of the facial nerve can cause a Bell's palsy. Other isolated cranial nerve palsies have been reported. Infiltration of the brain results in signs and symptoms predicated on the site of involvement. In rare instances, destruction of the posterior pituitary produces a picture of diabetes insipidus. Extensive localized cerebral atrophies have been noted. A lymphocytosis in the cerebrospinal fluid may be detected in instances of central nervous system involvement (36). All central nervous system manifestations are uncommon.

LIVER.—Miliary tubercles may be found in the liver on aspiration biopsy in approximately three fourths of the cases. This serves as an admirable source of histologic material for diagnostic purposes, but it may be quite difficult to differentiate between the granulomas of sarcoidosis and those caused by other agents (48). Although anorexia and malaise, commonly observed in sarcoidosis, may be attributed to hepatic involvement, more classic evidence of liver disease, such as jaundice, is unusual (49). In rare instances, either because of replacement of hepatic cells by diffuse granulomas and/or the development of fibrosis with healing, jaundice and signs of hepatic failure are noted. Whether the abnormal protein pattern of sarcoidosis represents hepatic involvement or a more subtle metabolic derangement is not known.

MISCELLANEOUS LESIONS.—The literature is replete with reports of the occasional finding of involvement of various organs in the course of sarcoidosis. While most of these are medical curiosities, they further corroborate the protean nature of the disease. Lesions have been noted in most of the endocrine glands and, with the exception of diabetes insipidus resulting from destruction of the posterior pituitary, usually are not responsible for symptoms. In contradistinction to tuberculosis, the adrenal gland is rarely, if ever, involved. Sarcoid lesions in the stomach, colon and small intestines have been noted on rare occasions. The latter may stimulate regional enteritis clinically and pathologically. It is not believed, however, that the two are related (50). In the lower genitourinary tract, the prostate, seminal vesicles, epididymis, tests, ovaries and uterus may be involved. Solitary nodules in the breast have been described. The reader is referred to the extensive monographs of Longcope and Freiman (31) and of Leitner (36) for further descriptions of these more esoteric findings.

DIAGNOSIS

To diagnose sarcoidosis with any degree of accuracy requires a careful evaluation and correlation of clinical features, roentgenologic findings and epidemiologic data, the application of laboratory tests and immunologic procedures, as well as confirmatory histologic evidence of sarcoidosis. The interpretation of even the latter may be fraught with error. Prolonged observation and careful study is required in many cases before the diagnosis can be made with any degree of finality.

Laboratory Data

Hematologic findings.—Unless there are abnormalities of associated thrombocytopenia, hemolytic anemia or leukopenia, as discussed above, there are no consistent aberrations in the hemogram. Leukopenia, which is not infrequent, is usually associated with splenomegaly but may occur in its absence. Eosinophilia from 8 to 20% has been recorded in approximately 15% of the cases. It would probably be detected more

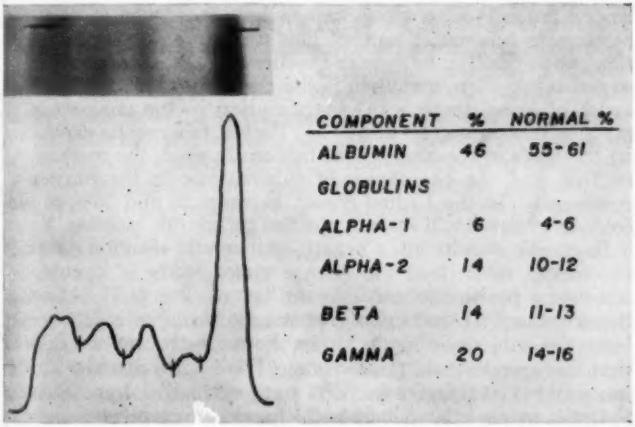


Fig. 14.—Electrophoretic pattern of serum from a patient with sarcoidosis.

frequently were serial differential counts performed. The erythrocyte sedimentation rate may be elevated, particularly in those patients who are febrile. An elevation of the total serum protein occurs in a significant number of patients, particularly during periods of activity. The globulins are elevated (75–80% of patients), and albumin is sometimes decreased. In some cases, total protein values are as high as 10 Gm./100 ml. The evidence of this abnormality varies in different series, but it is probable that changes will be found in nearly all cases if determinations are done at frequent intervals by electrophoretic methods. This technic uncovers the following abnormalities: a low albumin with an elevation of the alpha$_2$ and gamma fractions of globulins, producing the so-called "step pattern" (Fig. 14). The gamma globulins may contribute over 40% of the total and usually represent 25–30% (16% is upper limit of normal). The serum calcium is elevated in approximately 20–30% of the cases and is usually of no clinical significance. Hypercalciuria is detected more frequently and is a more significant finding. In a few patients, hyperuricemia has also been observed.

Skin Tests

Early in the study of sarcoidosis it was noted that there was, among patients with sarcoidosis, a high incidence of negative reactors to tuberculin testing. This was more apparent at that time when positive tuberculin reactions in the community were so much more frequent than is the case at present. In different series of cases, there is a wide variation in the percentage of positive tuberculin reaction (51). Part of this can be explained on the basis of the amounts of tuberculin used, the methods of reading and the prevalence of tuberculosis in the particular community. In the United States, between 25 and 35% of sarcoidosis patients will show a positive tuberculin reaction. From a diagnostic standpoint, a negative tuberculin reaction does not necessarily mean that the disease under study is sarcoidosis, nor does a positive tuberculin reaction rule it out. The cause of the increased frequency of negative tuberculin reaction has been the subject of much study. Formerly it was considered that this represented "positive anergy"—i.e., an extreme hyperimmunity to tuberculosis. The most attractive hypothesis is that this represents a deficit in the immunologic processes of the patient, whereby the skin has lost its ability to react to antigenic substances (51). British investigators (51, 52) have

claimed that an increased number of tuberculin reactors can be unmasked by the use of depot tuberculin or by the addition of cortisone to the skin-testing material. Indeed, a similar depressed reactivity to mumps virus, to pertussis vaccine and to a variety of cutaneous fungi has been noted in patients with sarcoidosis. Some groups utilize the Candida antigen diagnostically, considering a negative reaction as suggestive of sarcoidosis, since most normal individuals will react to this material (51). The fact that these patients have circulating antibodies to these respective antigens would seem to corroborate this. Similar findings of depressed skin reactivity is noted in Hodgkin's disease, and among other diseases.

KVEIM TEST.—Kveim, in 1941, demonstrated that the intracutaneous injection of a saline suspension of sarcoid lymph node into a patient with sarcoidosis resulted in the development of a papule within 1–4 weeks. Its histology was that of the sarcoid reaction. The Kveim reaction, as now used, is positive in the vast majority of cases of active disease (53). There are conflicting reports as to its significance, and much of the confusion results from the unpredictability of the antigen and from lack of its standardization. When the test is properly performed, the reaction is positive in nearly all cases of sarcoidosis, and there are few, if any, false positives reactions. The papule usually appears within 2–4 weeks and persists for many months. On rare occasions, 18 months may be required for its development. The concurrent administration of adrenal steroids may suppress its development. To be considered "positive," a Kveim reaction requires a biopsy, and the specimen must show all the classic features of the sarcoid tubercle. Bits of cotton and other foreign material will evoke a nonspecific foreign-body reaction which may cause much confusion; therefore, care in the preparation of the antigen and in its administration is essential.

BIOPSY

Even though all clinical features are consistent with sarcoidosis, the diagnosis cannot be made with a high degree of certainty without the demonstration of histologic changes compatible with the disease. Unfortunately, even biopsy findings are not completely diagnostic. The pathologist can only report "consistent or compatible with sarcoidosis," for other entities also evoke the "sarcoid reaction" (18). Enlarged peripheral lymph nodes, excluding those in the inguinal region, are an

excellent source of pathologic material, as are cutaneous lesions. In those instances where there is no such readily accessible material, the scalene fat pad containing lymph node may be used for biopsy. This material has been rewarding in 70–80% of patient suspected of having sarcoidosis. An aspiration biopsy of the liver will often reveal the characteristic tubercles. Less commonly used sites for biopsy are the lacrimal glands, muscles, conjunctivas, tonsils and bronchial mucosa. Sarcoid granulomas may be found in bronchial epithelium even in the absence of gross lesions. In many cases where positive material has not been found by these approaches, pulmonary biopsies have been resorted to with gratifying results.

Differential Diagnosis

As can be seen in Figure 7, there are several known etiologic agents that can evoke the clinical picture of sarcoidosis. Moreover, a variety of agents, animate and inanimate, are capable of inciting a histologic picture compatible with the sarcoid tubercle. Obviously, the patient with diffuse pulmonary infiltration, parotid enlargement, uveitis, punched-out lesions in the phalanges, peripheral adenopathy, cutaneous plaques, a positive reaction to node biopsy and a positive Kveim reaction has sarcoidosis—the disease of unknown etiology. But there are all shades of gray in clinical and laboratory features among the several entities to be considered in the differential diagnosis (27). The diseases that one must consider, and which most often cause confusion, are tuberculosis, histoplasmosis (and some other systemic mycoses) and beryllium disease (54). Less frequently, Hodgkin's disease, metastatic carcinoma, Sjögren's syndrome and certain specific infections (e.g., brucellosis) may pose difficulties. Careful consideration must be made of all facets (clinical, laboratory and epidemiologic) presented by the patient suspected of having Boeck's sarcoidosis before the disease can be categorically diagnosed or excluded. References to Tables 1, 2 and 3 will indicate some of the clues that may be useful.

COURSE

The varied clinical manifestations, dependent, as they are, on the unpredictable and scattered organ involvement, the remis-

sions and exacerbations, the long latent periods—all make it difficult to delineate a typical course for sarcoidosis. In general, the disease pursues a relatively benign course, with residual changes in the function of involved organs being minimal.

TABLE 1.—SCHEMATIC PRESENTATION OF RELATIVE FREQUENCY OF ORGAN INVOLVEMENT IN SARCOIDOSIS AND IN DISEASES WITH WHICH IT MAY BE CONFUSED
(Based on Clinical and Histopathologic Findings)

	SARCOIDOSIS	HISTOPLASMOSIS	TUBERCULOSIS	BERYLLIUM DISEASE
Lungs	++++	++++	++++	++++
Hilar nodes	+++	+	+	+
Peripheral lymph nodes	++++	++	+	+
Skin	++	±	±	+
Eyes	++	±	+	0
Liver	+++	++	+	±
Spleen	+++	++	+	+
Heart	++	0	0	0
Bones	++	±	++	±
Central nervous system	+	+	++	0
Salivary and lacrimal glands	+	0	0	0
Muscle	+	0	0	0

TABLE 2.—LABORATORY FEATURES WHICH MAY BE OF DIAGNOSTIC AID—SCHEMATIC PRESENTATION OF RELATIVE FREQUENCY

	SARCOIDOSIS	HISTOPLASMOSIS	TUBERCULOSIS	BERYLLIUM DISEASE
Hyperproteinemia	+++	+	±	+
Hyperglobulinemia	+++	+	+	+
Hypercalcemia	++	0	0	+
Hypercalciuria	++	0	0	+
Eosinophilia	++	+	0	±
Leukopenia	+	+	±	±

Several representative cases are presented below to illustrate the vagaries of the clinical course of sarcoidosis.

CASE 1.—A 25-year-old white farmer was found, on a routine chest x-ray, to have enlargement of both hilar nodes and scattered miliary lesions in the lungs. He was completely asymptomatic. A biopsy of the epitrochlear node was consistent with sarcoidosis. Within 6 months the nodes had regressed; and 3 years after discovery of the lesions, the chest film was completely clear. During this time the only symptom was mild fatigue.

Case 1 illustrates the type of benign illness that may be found.

CASE 2.—A 30-year-old Negro laborer developed pain and photophobia in both eyes. He was found to have generalized lymphadenopathy, scattered nodules over the face and shoulders and a palpable spleen and liver. There was extensive acute iridocyclitis in both eyes.

TABLE 3.—PRINCIPAL EPIDEMIOLOGIC FEATURES NOTED IN SARCOIDOSIS AND IN DISEASES WITH WHICH IT MAY BE CONFUSED

	SARCOIDOSIS	HISTOPLASMOSIS	TUBERCULOSIS	BERYLLIUM DISEASE
Age	Young adults; rare in children	Any age	Any age	Adults
Race	More in nonwhites	No difference	Slightly more in nonwhites	No difference
Occupation	Outdoor workers	Not relevant	Not relevant (contacts)	Beryllium and allied industries
Geographic	North Temperate Zone (eastern United States)	Principally central United States	World wide	Scattered with industry
Urban or rural	More rural	Both	Urban	Depends on location of industry
Socioeconomic	Not pertinent	Not pertinent	Low-income groups	Not pertinent (exposure)

A diffuse reticular pattern scattered throughout the lungs was found in the chest x-ray. He was seen before adrenal steroids were available and was treated symptomatically. Within a year he was totally blind. Within 5 years the skin lesions and lymphadenopathy had receded but residual pulmonary fibrosis persisted.

Case 2 is an example of permanent functional damage resulting from particular organ involvement.

CASE 3.—A 46-year-old white woman had several bouts of hemoptysis, episodes of fever and production of purulent sputum over a pe-

riod of 5 years. Her spleen was palpable. By x-ray and bronchographic studies, she was found to have extensive pulmonary fibrosis and bronchiectasis. The serum globulins were elevated. A biopsy of the liver demonstrated classic sarcoid tubercles. She had migrated to this country from Denmark 30 years previously.

The above patient probably had sarcoidosis for many years, and, although it was still active, healing of the pulmonary lesions had produced fibrosis and subsequent changes of bronchiectasis.

CASE 4.—A 42-year-old Negro farmer was diagnosed as having sarcoidosis at age 25. At that time, cough and dyspnea were his chief complaints. A diffuse infiltrative process extending from both hilar regions was seen on chest x-ray. Biopsy of a cervical lymph node was consistent with sarcoidosis. Fibrosis increased until at age 35 there was diffuse pulmonary fibrosis with numerous blebs. His activities were markedly limited. Over the next 7 years, he was a "pulmonary cripple" with orthopnea and bouts of pneumonia, and he was bedridden. He developed signs of right-sided heart failure, and died 2 years later during one of the bouts of pulmonary infection. No evidence of sarcoidosis was found at autopsy, and the functioning lung tissue was almost entirely replaced by fibrosis and emphysematous blebs. The right ventricle was thickened and dilated.

In the foregoing instance, death, although not caused directly by sarcoidosis, resulted from the permanent structural changes in the lungs that resulted from healing of the sarcoid lesions. Cor pulmonale was part of the sequence of events.

PROGNOSIS

The ultimate outcome of the patient with sarcoidosis is highly unpredictable. As mentioned, in most cases it represented a relatively benign disease (55). Conflicting data make it difficult to state, with any degree of accuracy, the percentage of patients who later develop pulmonary tuberculosis. It is certainly not of the order of 30%, as some writers have indicated (31). However, it is greater than the incidence of tuberculosis in the general population. A follow-up study (after 5 years) made on 540 veteran patients indicated that less than 15% died of tuberculosis. Most patients recover completely with only minor functional residua. Most of the deaths are attributable to pulmonary fibrosis, cor pulmonale and superimposed infection.

Since it is almost impossible to date the onset of the disease in most cases, it becomes difficult to state how long is required for it to become quiescent. This dilemma is further added to by the fact that assessment of "activity" is fraught with error. Most

patients who commence with erythema nodosum and the bilateral hilar lymphadenopathy syndrome have "healed" completely within 2 years. The other manifestations may require 10 or more years to "burn out."

TREATMENT

The oft-alluded-to capricious nature of the course of sarcoidosis makes a controlled evaluation of its therapy difficult. As is true of all diseases of unknown origin, a host of agents and technics have been introduced and later abandoned. These will not be reviewed here. Suffice it to say that bed rest is indicated only during acute febrile states, when systemic symptoms such as profound weakness and lassitude can be treated beneficially.

The various antituberculosis drugs have no place in the primary treatment of sarcoidosis. Enough studies have corroborated their ineffectiveness in the course of the disease except where tuberculosis does exist (56).

The various adrenal steroids have a definite beneficial effect on the sarcoid lesions. Analogous to rheumatoid arthritis, the granulomatous inflammation is suppressed, as are symptoms associated therewith. The sarcoid tubercle changes to a more nonspecific inflammatory reaction. Withdrawal of these drugs is followed by a recrudescence, the severity depending on the particular cycle of the disease (wholly unpredictable). In those cases where the disease has been allegedly "cured" by such therapy, it is likely that an underlying spontaneous remission may have occurred anyway (56). Particularly is this true in the subacute varieties of the disease.

The systemic administration of adrenal steroids to those patients with acute iridocyclitis is mandatory and is usually instrumental in saving vision. In the patient who is asymptomatic or who is only slightly incapacitated by the disease—be it pulmonary, cutaneous, articular, etc.—steroids may be contraindicated. True, lesions will regress, only to recur later, and the treacherous side effects of long-term steroid therapy are added to a relatively benign clinical picture.

Contrariwise, when there is moderate impairment of pulmonary function, the use of steroid therapy may be beneficial. When the disease is rapidly progressive or there is marked impairment of pulmonary function, its use is mandatory. In those cases with involvement of the central nervous system or

myocardium, or in those with significant hypercalcemia and hypercalciuria, steroid therapy is also mandatory. The duration of therapy is variable and is often a matter of trial and error. Several weeks are needed to be certain that no effect will be obtained. By and large, a course of therapy should exceed 2–3 months.

There are conflicting and emotional views as to whether patients receiving steroid therapy for sarcoidosis should be "covered" with antituberculous drugs. It is the belief of the authors that, unless there is strong evidence that tuberculosis coexists, such antibiotic therapy is unnecessary.

SUMMARY

This attempt to correlate some of the pertinent clinical, laboratory and experimental features of sarcoidosis has been drawn largely from our personal experiences with patients with this disease. Wherever it has seemed contributory, the viewpoints of others have been summarized or quoted. Nevertheless, the appraisal of a disease process which presents such a variable clinical picture makes it difficult, if not impossible, to treat the issues dogmatically or exhaustively. Emphasis has been placed on those facets of the disease which appeared, to us, to be most important or to those which have been, to some extent, neglected. Until the cause of the disease is known definitely, clinical judgment supplemented by laboratory and histologic findings will be the only basis for establishing diagnosis, selecting therapy and estimating prognosis.

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